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PHARMACY SERIES, No. 3

GELSEMIUM

A Study that Embodies the Recent Work of
PROFESSOR L. E. SAYRE,
LAWRENCE, KANSAS,

Together with Fragments of a Paper Read by
Him Before the American Pharmaceutical
Association, Richmond, Virginia, 1910.

Accompanied by a Plate of Physiological Tra-
cings by Professor H. W. Emerson.

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- No. 17. Pharmacy Series, No. 3.
Gelsemium. A study that embodies the recent work of Prof. L. E. Sayre, Lawrence, Kansas, together with fragments of a paper read by him before the American Pharmaceutical Association, Richmond, Virginia, 1910, accompanied by a plate of physiological tracings by Prof. H. W. Emerson.

Bibliographical Contributions from the Lloyd Library

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Mycological Writings of Mr. C. G. Lloyd

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Mycological Notes, Old Species Issue, No. 1, 1908.
Mycological Notes, Polyporoid Issue, No. 1 to No. 3, 1908-1910.
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The Genera of the Gastromycetes, 1902.*
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The Lycoperdaceae of Australia, New Zealand, and Neighboring Islands, 1905.*
The Tylostomeae, 1906.
The Nidulariaceae, 1906.
The Phalloids of Australasia, 1907.
Synopsis of the Known Phalloids, 1909.*
Synopsis of the Genus Hexagona, 1910.*
Synopsis of the Sections Microporus, Tabacinus, and Finales of the Genus Polystictus, 1910.

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GELSEMIUM AND ITS ACTIVE CONSTITUENTS.*

It is generally conceded by the medical profession that Gelsemium is one of the most important drugs of our *materia medica*, and yet, it is interesting to note, there is some confusion regarding its action. As a consequence there must be some uncertainty and lack of confidence in its therapeutical application. Much of this arises from ignorance of its chemical constitution. If one knows exactly the nature of the chemical constituents of a given drug, he can better comprehend its therapeutic action, more intelligently apply it, and with more confidence select from its various preparations—and thus obtain more definite results. Not until chemists informed practitioners of the nature of the constituents of aconite, showing, among other things, that in the drug there existed not only aconitine, but other possibly antagonistic principles, and that the important alkaloid, aconitine, was quite susceptible to hydrolysis, was it quite possible for physicians to prescribe its preparations satisfactorily. A closer study of the constituents of Gelsemium, in like manner, promises to yield the same kind of beneficial result. Gelsemium has seemed to have, in the hands of many physicians, two different specific actions; the one, if not antagonistic, seems to interfere with, or interpose, the action of the other. One of these actions may be characterized as a muscular paralytic action through the spinal cord, and the other a circulatory depressant action through the vagus center, slowing the heart and lowering blood pressure. It is this latter action for which the drug is highly prized. It acts, in this heart reduction and in this reduction of blood pressure, quite differently from aconite, and we are inclined to think more satisfactorily if the proper principles of the drug are utilized.

It has not been determined exactly what are the specific actions of the different principles of Gelsemium. This is due partly to the fact that they have not been separated and thoroughly purified—the different principles are so apt to combine that their entire separation, in the state of purity, is quite difficult. When these principles have been isolated and purified, and their physiological action studied, physicians will better know when and how to employ the drug and select its preparations.

The present paper will endeavor to throw some light upon the organic principles of this interesting drug, and, in a preliminary way, to discuss their physiological action—thus paving the way for future work.

*Some of the material in this article was embodied in a paper read before the American Pharmaceutical Association, Richmond, Va., 1910, and will appear in its annual proceedings.

The two important constituents of the drug have been named *Gelsemine* and *Gelseminine* respectively. The last named alkaloid has not as yet been satisfactorily defined, as it has not been sufficiently purified.

What has been recognized hitherto as gelseminine is a soft, resinous, alkaloidal residue remaining after gelsemine hydrochloride has been crystallized from alcoholic solution of the mixed alkaloids. Thompson¹ first announced this as a second alkaloid. Cushny regarded it as a powerful poison resembling coniine. Whether this is a distinct alkaloid, a polymerized form of gelsemine, a mixture of various uncrystalline principles of unknown composition, has not been determined. Our work recently has indicated that it is a complex substance. We have been able to separate it into at least two distinct bodies, having different solubilities and different reactions with agents.

The crude gelseminine for our work was obtained by the Thompson method and by two different modifications of his process, as follows:

METHOD A.

A one-fourth portion of a soft alcoholic extract obtained from 50 pounds of drug² was treated with a 2 per cent solution of H_2SO_4 , the acid solution thoroughly washed with chloroform by which all the gelsemic acid seemed to be removed. The acid solution was made alkaline and shaken with ether-chloroform (5 to 1) until exhausted and the separated ether layer washed with 2 per cent hydrochloric acid. On concentrating this liquid in vacuo, the residue consisted mostly of soft, resinous-like, reddish, gelseminine hydrochloride; seemingly very little or no white alkaloid gelsemine was present.

METHOD B.

In this case the soft extract ($\frac{1}{4}$ portion) was first treated with an equal bulk of lime and dried, after which it was treated with 2 per cent H_2SO_4 . The acid solution was washed with chloroform and the subsequent treatment was precisely similar as in Method A, using the solvent in the same order. The final acid aqueous washing of the chloroform-ether solution of the alkaloids was concentrated in vacuo to small volume. The evaporation was continued to dryness and the dry product powdered. The powder, which was quite dark, was treated with U. S. P. alcohol. This left 2.1 Gm. of the colorless salt, gelsemine hydrochloride.

The separated alcoholic solution was concentrated and set aside to crystallize, but no more crystals appeared. The concentrate corresponded to Thompson's gelseminine. It was a red, soft, gummy, resinous mass, with strong alkaloidal reaction, and had a very bitter taste.

METHOD C.

A third portion, consisting of the remaining half of the original extract, after making alkaline, was extracted with benzol. The solution was filtered and shaken out with 2 per cent H_2SO_4 ; the acid solution was then washed with chloroform to remove gelsemic acid. The subsequent treatment with the immiscible solvents was the same as in Method A, the liquids being used in the same order. The acid solution was then concentrated in vacuo to small volume and set aside to crystallize.

¹Pharmaceutical Era, 1887, p. 3.

²Proceedings American Pharmaceutical Association, 1909, p. 902.

Colorless crystals of gelsemine hydrochloride separated, which, after washing with U. S. P. alcohol and drying in vacuum desiccator, weighed 11.5 Gm. This method gave the largest yield of gelsemine hydrochloride. The liquid from which the crystals were removed gave, on concentration, a residue characteristic of Thompson's gelsemine hydrochloride.

All of these products (crude gelseminine) from Methods A, B, and C were separately subjected to further examination in the hope of obtaining more definite information concerning this soft, resin-like alkaloid.

It may be well to state in passing that crude gelseminine gives with manganic oxide and H_2SO_4 a purple color, while gelsemine gives a cherry-red. The final color of gelsemine merges into green, fading to a yellow.

The suspicion has been entertained that the so-called gelseminine consists of possibly a mixture of coloring matter and another alkaloid persistently combined therewith. The persistent "combination" referred to has not thus far been possible to break up by any ordinary means of alkaloidal separation. Thompson's gelseminine is, by another theory, a derivative of the colorless alkaloid or of esculin, having somewhat the same relation to gelsemine, as does chinoidine to quinine. Indications seem to be that gelseminine, when obtained pure, will prove itself to be a colored alkaloid, producing colored salts.

It might be well to state here also that the physiological tests of the crude gelseminine hydrochloride, formerly produced by us, indicate that it differs from gelsemine, in being about ten times more toxic than gelsemine.³ Cushny, as before stated, found that its action was very similar to that of coniine, was more depressant to the central nervous system, and had mydriatic properties, but as such was too irritating for practical use. Some authorities state that the effects of the crude drug are mainly due to the uncrystalline alkaloid gelseminine, and not the crystalline gelsemine. In order to study the constitution of this gelseminine, it is evident that it must be brought to a more definite physical and chemical condition. In attempting to do this, the three crude gelseminines, A, B, and C, as above stated, were made the starting point.

Examination of Crude Gelseminine (A).—This consisted of a reddish colored product, which when dried in a current of warm air weighed 19.92 Gm. This product, by solution in acidulated water, precipitation by ammonia, washing out by immiscible solvents, twice repeated, yielded crude crystals of the colorless gelsemine hydrochloride, which when purified weighed 0.6556 Gm. It was thus made clear that a fair proportion of the so-called crude gelseminine (A) consisted of the alkaloid gelsemine.

All attempts to purify or crystallize the remaining soft, resinous, alkaloidal substance from which the gelsemine hydrochloride had been separated was of no avail. It persistently remained as a colored mass which dried, in a thin layer, into a hygroscopic, scaly salt.

Examination of Crude Gelseminine (B).—Treated with absolute alcohol it was found to be not entirely soluble. 6.5 per cent remained undissolved, but the insoluble portion could not be deprived of its coloring matter. It was probably a mixture of gelsemine and gelseminine.

1.6355 Gm. of crude gelseminine (B) containing 17 per cent of moisture, corresponding to 1.2574 Gm. of dried material, was precipitated from an acidulated solution by means of ammonia in excess.

The liquid containing the suspended alkaloid was transferred to a filter and continuously washed with ammoniacal water until the washings ceased to show presence of alkaloid.⁴ The residue on the filter

³Dr. E. D. Reed, Pharmacologist. See Proceedings A. Ph. A., 1908, p. 855.

⁴We have noted before that some of the alkaloids of gelsemium seemed to be remarkably soluble in ammonia.

was then transferred to ammoniated water and allowed to macerate for several hours. The liquid was transferred to a filter and again washed as before. The insoluble precipitate was carefully dried in a vacuum desiccator. It weighed 0.4752 Gm., thus indicating a distinct separation. One of these separated products (insoluble in ammonia) we designate as gelseminine (B_1), the other (B_2).

The ammoniacal filtrate was separated into three portions; the first portion passing through the precipitate and filter was of a pinkish color; the second portion was less colored, and the third portion colorless. These three solutions were separately dried in a vacuum desiccator, which was supplied with a current of air made dry by a battery of Woulfe bottles containing sulphuric acid, and finally a U-tube of calcium chloride, a partial vacuum being maintained. Practically dry products were thus obtained; Gelseminine, B_2 (Gelsemoidine [?]).

The first residue⁵ was brittle and of a reddish color. The second residue was of a lighter yellow, and the third was practically colorless. All three were alkaloidal—the third, colorless residue, was also alkaloidal and contained insoluble material. The total weight of the alkaloid soluble in ammonia was 1.1584.

(B_1): The precipitate insoluble in ammonia was first dissolved in dilute sulphuric acid, transferred to a separator, made alkaline with ammonia; the alkaline solution washed with chloroform, which readily extracted the colored alkaloid. The chloroform solution was transferred to a second separator, and after washing with distilled water was extracted with dilute hydrochloride acid. This last washing removed practically all of the color and the alkaloid. This was placed in a vacuum desiccator and dried the same as the former solution. The weight was 0.4572 Gm.

It should be noted here that the alkaline aqueous reddish solution (B_2) when washed with chloroform, yielded practically no color or alkaloid, the coloring matter as well as alkaloid remaining in the alkaline fluid. On the other hand, the alkaloid from B_1 , with its red color was readily transferred to chloroform when its solution, made alkaline, was shaken out by that solvent.

Examination of crude Gelseminine (C).

Treated with absolute alcohol, this was found to be entirely soluble.

1.435 Gms. of Gelseminine (C) containing 10 per cent of moisture was taken, precipitated by ammonia, and succeeded by the same treatment as that to which the former product (B) was subjected. The precipitate insoluble in ammoniacal water weighed 0.0835 Gm. (5.81 per cent), and had the same characteristics as the former insoluble precipitate.

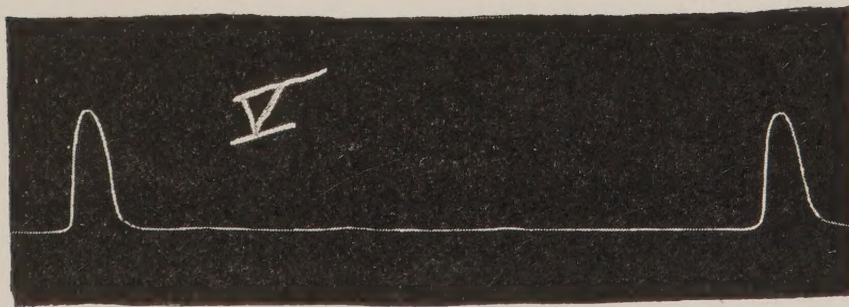
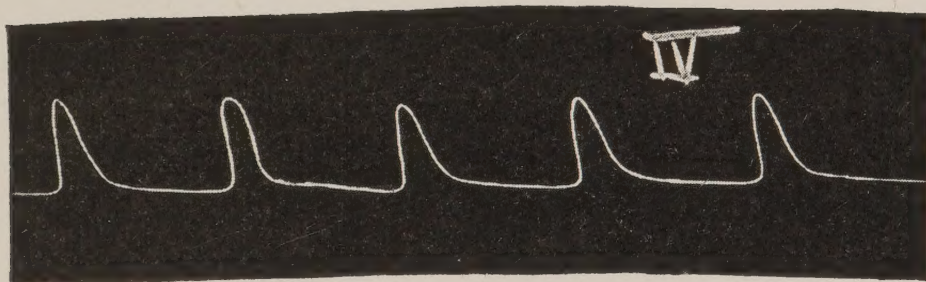
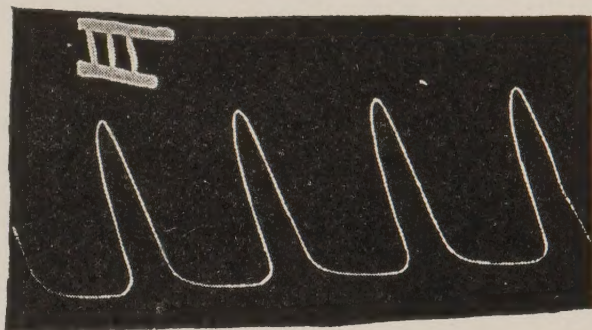
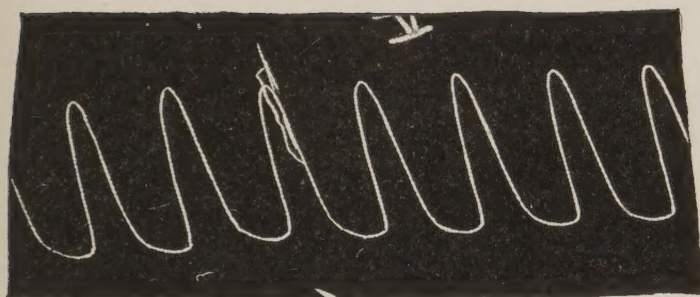
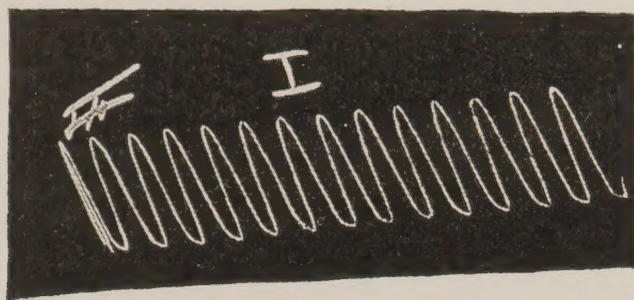
PHYSIOLOGICAL EXPERIMENTS.

To study the effect of the three different principles (gelsemine, "gelsemoidine" (?) and gelseminine) on the circulation and to make at least a rough comparison of their physiological activity, a standard solution of each was made so that each $\frac{1}{10}$ of a cc. represented 0.001 Gm. of the alkaloid. Fractions of these solutions, or portions of a milligram of the alkaloid, or alkaloidal salt, were injected into the lymph sac of a frog. These were of about the same body weight; their heart-beats, at the beginning of the experiment, were about the same—60 beats per minute. The quantity of the alkaloid, or its solution, was varied so as to produce a given result—noting the quantity as well as the time to produce this. In the case of Gelsemine and Gel-

⁵This was necessarily contaminated with a small proportion of $NH_4 Cl$.

PHYSIOLOGICAL ACTION OF GELSEMININE

Weight of frog, 33 Gm. Normal heart rate, 65.



For all of these physiological experiments I am indebted to my associate, Professor H. W. Emerson. (See pages 3 and 4.)

semoidine (soluble in ammonia), the heart-rate was reduced to 5 beats per minute, and in the case of Thompson's crude Gelseminine and purified Gelseminine (insoluble in ammonia), the heart-beat was reduced to zero. The following results were thus obtained:

1—Gelsemine hydrochloride: 0.0018 Gm. reduced the beats to 5 per minute in 1 hour and 30 minutes.

2—Gelsemoidine (soluble in ammonia): 0.0032 Gm. reduced the beats to 5 in 10 hours and 30 minutes.

3—Thompson's Gelseminine (crude alkaloid): 0.0015 Gm. reduced the pulsations to zero in 5 hours and 40 minutes.

4—Gelseminine purified (insoluble in ammonia): 0.0011 Gm. reduced pulsations to zero in 4 hours.

Sphigmographic tracings were made which graphically confirm the opinion that:

1—Gelsemine hydrochloride, contrary to statements formerly made by pharmacologists, has an inherent power as a heart depressant, preceded by a period of excitation.

2—The alkaloid soluble in ammonia (B_2), which if found to be a separate alkaloid we may name gelsemoidine, is less powerful as a heart depressant than gelsemine, and it is suspected of a paralytic action. To be fully determined later.

3—The alkaloid gelseminine (insoluble in ammonia), is a typical heart depressant.

A reproduction of the tracings is perhaps unnecessary, but those tracings showing the progressive action of the purified gelseminine may be of value. The gradual slowing of the pulsation, in direct proportion to the alkaloid administered, is quite marked, and with this action there seems to be no muscular twitching, as in gelsemoidine, showing a purely circulatory depressant action.

10.40 A. M. Injected 0.2 Cc. of the above solution.
 10.55 A. M. Heart rate 60. 11.10 A. M. Heart rate 54. 11.15 A.
 M. Heart rate 49. 11.30 A. M. Heart rate 40.
 11.30 A. M. Injected 0.4 Cc. of the solution.
 11.45 A. M. Heart rate 30. 12.00 M. Heart rate 28. 12.40 P. M.
 Heart rate 26. 1.05 P. M. Heart rate 23.
 1.10 P. M. Injected 0.5 Cc.
 1.40 P. M. Heart rate 10. 1.52 P. M. Heart rate 8. 1.57 P. M.
 Heart rate 6. 2.20 P. M. Heart rate 5. 2.40 P. M. Heart ceased to
 beat.

To determine relative toxicity:

Four frogs of about equal weight—weights from 30 to 35 Gm.—
 were taken:

EXPERIMENT 1.								
	10.00 A. M.	10.30 A. M.	11.00 A. M.	11.30 A. M.	12.30 P. M.	3.00 P. M.	8.00 P. M.	8.00 A. M.
Prep. 1.....	0.7 Cc.	Normal	0.5 Cc.	Very weak	Dead.			
Prep. 2.....	0.7 Cc.	Nearly normal	0.5 Cc.	Weak.	Very weak.	Very weak.	Very weak.	Dead.
Prep. 3.....	0.7 Cc.	Nearly normal	0.5 Cc.	Excited.	Very weak.	Very weak.	Dead.	
Prep. 4.....	0.7 Cc.	Quite depressed.	0.5 Cc.	Dead.				

EXPERIMENT 2.									
	10.00 A. M.	10.30 A. M.	11.00 A. M.	11.30 A. M.	12.00 M.	3.00 P. M.	6.00 P. M.	8.00 A. M.	10.00 A. M.
Prep. 1.	0.1 Cc.	Normal.	0.1 Cc.	Depressed.	0.1 Cc.	Depressed.	Dead.		
Prep. 2.	0.1 Cc.	Normal.	0.1 Cc.	Excited.	0.1 Cc.	Excited.	Depressed.	Dead.	
Prep. 3.	0.1 Cc.	Normal.	0.1 Cc.	Slightly depressed.	0.1 Cc.	Depressed.	Very weak.	Dead.	
Prep. 4.	0.1 Cc.	Normal.	0.1 Cc.	Depressed.	0.1 Cc.	Depressed.	Very weak.	Nearly dead.	Dead.

EXPERIMENT 3.										
	10.00 A. M.	10.30 A. M.	12.00 M.	3.00 P. M.	6.00 P. M.	8.00 A. M.	10.00 A. M.	12.00 M.	4.00 P. M.	6.00 P. M.
Prep. 1.	0.1 Cc.	Normal	Normal	0.1 Cc.	Depress'd	Dead				
Prep. 2.	0.1 Cc.	Excit'd	Excited	0.1 Cc.	Excited	Nearly Normal	0.1 Cc.	Excited	Dead	
Prep. 3.	0.1 Cc.	Normal	Slightly excited	0.1 Cc.	Depress'd	Slightly depressed	0.1 Cc.	Very depressed	Very depressed	Dead
Prep. 4.	0.1 Cc.	Normal	Normal	0.1 Cc.	Depress'd	Normal	0.1 Cc.	Depress'd	Depress'd	Slightly depressed

ANALYSIS (COMBUSTION) OF GELSEMINE HYDROCHLORIDE.

The combustions of Gelsemine Hydrochloride were carried out in the usual way, using a silver spiral to take care of the chlorine and a reduced copper spiral to break up nitrogen oxide compounds.

Combustions for carbon and hydrogen:

No. 1. Carbon 66.48 per cent. Hydrogen 6.46 per cent.

No. 2. Carbon 66.34 per cent. Hydrogen 6.41 per cent.

Combustions for Nitrogen:

No. 1. Nitrogen=5.68 per cent.

No. 2. Nitrogen=5.59 per cent.

Carius Method for determination of chlorine:

No. 1. Chlorine=13.00 per cent.

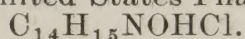
No. 2. Chlorine=13.60 per cent.

Oxygen by Differences:

No. 1. —7.78.

No. 2. —8.66.

Formula for Gelsemine Hydrochloride, using the atomic weights of United States Pharmacopœia. $H=1$.



Percentage of

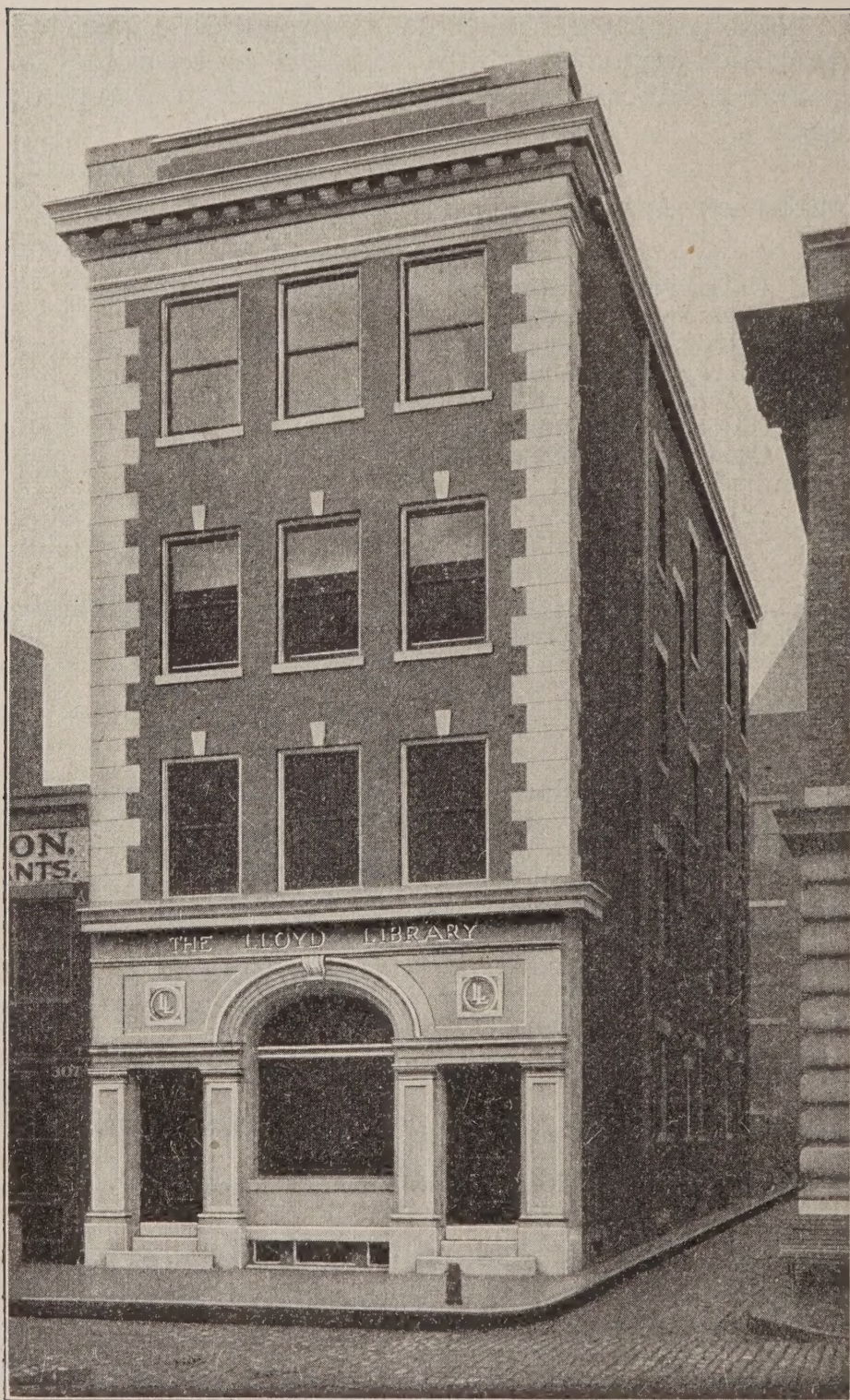
II.

Above Formula.	Obtained by Combustion.
C=67.307 per cent.....	$\left\{ \begin{array}{l} 66.48 \text{ per cent.} \\ 66.34 \text{ per cent.} \end{array} \right.$
H= 6.458 per cent.....	$\left\{ \begin{array}{l} 6.46 \text{ per cent.} \\ 6.41 \text{ per cent.} \end{array} \right.$
N= 5.623 per cent.....	$\left\{ \begin{array}{l} 5.68 \text{ per cent.} \\ 5.59 \text{ per cent.} \end{array} \right.$
O= 6.410 per cent.....	$\left\{ \begin{array}{l} 7.78 \\ 8.66 \end{array} \right\} \text{ By difference.}$
Cl=14.202 per cent.....	$\left\{ \begin{array}{l} 13.00 \\ 13.60 \end{array} \right\} \text{ By Carius.}$

The formula then for the alkaloid would be $C_{14}H_{15}NO$.

It will be noted that this is a different molecular formula for this alkaloid than that obtained by Thompson and Gerrard (Phar. Era, Jan. 1887, p. 3).





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